Rejection of claims 1-5, 8, 12-14 and 16 under 35 U.S.C. §102

Claims 1-5, 8, 12-14 and 16 remain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Bronstein et al., U.S. Patent No. 5,849,495.

The Office Action cites an embodiment of the Bronstein disclosure that allegedly anticipates claims 1-5, 8, 12-14, 16 and 18. The Office Action dated August 17, 2000, states that the embodiment of Bronstein et al. comprising the Hybritech Prostate Specific Antigen (PSA) kit, containing three different polypeptides, is used to determine the presence and amount of PSA in a sample. The three polypeptides are a PSA standard, an alkaline phosphatase-labeled mouse anti-PSA antibody and an anti-PSA capture antibody immobilized on a bead.

The Office Action dated August 17, 2000 states that the association of the alkaline phosphatase-labeled antibody with two different substrates resulted in the production of fluorescence and energy transfer from one modified component to another.

The Office Action dated April 19, 2001, states "[t]he two polypeptides used in the Hybritech Prostate Specific Antigen (PSA) assay are both associated with a label, specifically one is conjugated, covalently labeled with alkaline phosphatase and the other a bead. One of the polypeptides was contacted with an agent that was capable of covalently modifying the polypeptide to include a detectable label prior to assaying the modification of the association of the two polypeptides."

The Office Action dated April 19, 2001 also states, " 'the term 'modification' [as used in the instant application] may also include binding of one or more molecules of test sample to a polypeptide.' Clearly the assay that measures the presence of PSA in a test sample through binding of first and second polypeptides associated with one or more PSA molecules."

Applicants traverse this rejection, as this embodiment of Bronstein et al. does not describe the invention as claimed.

Claim 1 and dependent claims 2-5, 8, 12-14 and 16 claim "a method for **detecting covalent modification of a polypeptide** by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first**

polypeptide and said binding partner polypeptide; b) immobilizing the first polypeptide to a physical support; c) contacting the immobilized polypeptide with the second polypeptide; d) contacting said immobilized polypeptide and said binding partner polypeptide with said sample; and e) assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide."

The specification defines modification at p. 4, lines 6-13 as follows:

> Modification of a polypeptide may include proteolysis (proteolytic cleavage), phosphorylation, dephosphorylation (phosphatase), acylation (for example fatty acylation such as farnesylation, geranylgeranylation, myristoylation, palmitoylation), glycosylation, ubiquitination, prenylation, sentrinisation, ADP-ribosylation, or the reversal of these processes where these are possible. Preferably, the immobilised polypeptide may be a substrate for one or more of these enzymatic activities. The term 'modification' as used herein may also include the binding of one or more molecules of the test sample to a polypeptide.

It is also stated in the specification at p. 7, lines 22-24, "a polypeptide is susceptible to 'modification' if it is capable as serving as a substrate for one or more modifying enzymes in accordance with the present invention."

It is also stated in the specification at p. 9, lines 6-11, "[c]learly, a polypeptide which is susceptible to 'modification' may be subject to or may be the target of modification by any 'modification enzymes' such as proteases, kinases, phosphatases, farnesyl transferases, ADP-ribosylating enzymes, glycosylating enzymes, prenylating enzymes, geranylgeranyl transferases, ubiquitinating enzymes, sentrisation enzymes, fatty acylation enzymes, myristoylation enzymes, palmitoylation enzymes or any other polypeptide modifying enzyme."

Covalent modification is referred to in the specification at p. 97, line 21-p. 98, line 8. Applicants submit that one of skill in the art would reasonably accept that covalent modification refers to the covalent addition or removal of a group, that is the formation or destruction of a covalent bond. It is well-known in the art that a covalent bond refers to a strong bond (i.e., an energy of 15-170 kcal/mole) that is extremely stable but can be broken or rearranged by the activity of an appropriate enzyme.

It is stated in Molecular Biology of the Cell, 1994, Alberts et al., Garland Publishing, Inc., 50f, "[a] covalent bond forms when two atoms come very close together and share one or more of their electrons."

In contrast, non-covalent bonds are usually classified as ionic bonds, hydrogen bonds and van der Waals attractions.

The Examiner asserts that the two polypeptides disclosed in the embodiment of Bronstein et al., comprising the PSA detection kit, are the two anti-PSA antibodies.

Applicants submit that Bronstein et al. teach a PSA immunoassay wherein an alkaline phosphatase conjugated mouse anti-PSA antibody and a capture anti-PSA antibody are incubated with a sample, presumably comprising PSA. The two anti-PSA antibodies do not bind to each other directly, but rather associate via binding to PSA. Applicants also submit that covalent modification of at least one of the two anti-PSA antibodies does not result in modulation of the association of the two polypeptides, and is not required for this association, as claimed in amended claim 1.

It is well known in the art that binding of an antigen, to an antibody is mediated by non-covalent interactions. It is stated in Alberts et al., supra, at p. 1211, [t]he binding of an antigen to antibody, like the binding of substrate to an enzyme, is reversible. It is mediated by the sum of many relatively weak **noncovalent** forces, including hydrophobic and hydrogen bonds, van der Waals forces, and ionic interactions. Binding of PSA to an anti-PSA antibody would, therefore, not comprise covalent modification of the antibody.

Thus, in view of the above, Applicants submit that the Bronstein patent does not teach all of the limitations of amended claim 1. Neither of the anti-PSA antibodies taught in the embodiment of Bronstein et al. discussed above, are covalently modified in a manner that results in modulation of the association of the two antibodies, as required by amended claim 1.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. 102(e) rejection of claims 1-5, 8, 12-14 and 16 in view of Bronstein et al.

Rejection of Claims 1-7 and 14-15 under 35 U.S.C. §102(b)

Claims 1-7 and 14-15 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Tsien et al., U.S. Patent No. 5,439,797 (the '797 patent).

The Office Action dated August 17, 2000 states that the '797 patent discloses and claims a method of determining the concentration of an analyte in a sample, the method "carried out by utilizing first and second polypeptides that will associate with each other depending upon the presence, absence or amount of analyte present in the sample." The Office Action dated August 17, 2000 states further that both the first and the second polypeptides are fluorescently labeled in the '797 disclosure, that "the modification of the association of the first and second polypeptides is accomplished through fluorescence resonance energy transfer," and that the '797 disclosure teaches one of the polypeptides immobilized on a bead, concluding that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

The Office Action dated April 19, 2001 states, "[t]he claim limitation 'covalent modification' is recited in the 'providing step', a step prior to the polypeptides being contacted with each other. No covalent interactions are required in claim 1. The covalent modification argued is not commensurate in scope with the now claimed invention that does not require that a covalent modification take place; the claim limitation defines a conditional relationship if a covalent modification is introduced to one of the two polypeptides." Applicants respectfully disagree.

Amended claim 1 claims "a method for detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**; b) immobilizing the first polypeptide to a physical support; c) contacting the immobilized polypeptide with the second polypeptide; d) contacting said immobilized polypeptide and said binding partner polypeptide with said sample; and e) assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide.

Applicants submit that the '797 patent does not teach "a method for detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is

detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**", as required by claim 1 as amended. Specifically, neither of the polypeptides of the '797 disclosure is covalently (i.e., enzymatically) "modified," but rather the polypeptides bind to each other only in the presence of cAMP. Support for the "covalent" modification language of amended claim 1 is found on page 97, line 21 to page 98, line 8. Further, it is known in the art that all enzymatic reactions are covalent, based upon the definition of an enzyme:

> "A protein produced in a cell and capable of greatly accelerating by its catalytic action the chemical reaction of a substance (the substrate) for which it is often specific." (page 448, Dorland's Illustrated Medical Dictionary, 26th Ed., 1985, W.B. Saunders Co., Philadelphia; emphasis added; see Exhibit A filed with Applicant's response to the Office Action dated August 19, 2000)

Applicants submit that claim 1, as amended, requires that at least one of the polypeptides of the polypeptide pair of claim 1 must be susceptible to covalent modification wherein the covalent modification modulates the association of the polypeptide with the other member of the polypeptide pair.

It is stated in the specification at p. 22, lines 1-2, "[a]ccording to the invention, any two amino acid sequences capable of interacting with each other in a modification sensitive manner may be employed. Twelve examples of polypeptide pairs wherein covalent modification of one polypeptide of the pair results in modulation of the association of the polypeptides of the pair are presented in Examples 1-12 of the specification. Thus, Examples 1-12 of the instant application disclose twelve examples of a "polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**", as required by amended claim 1.

Tsien et al. do not teach such a polypeptide pair.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. 102(b) rejection of claims 1-7 and 14-15 in view of the '797 patent.

Rejection of Claims 1-7 and 14 under 35 U.S.C. §102(b)

Claims 1-7 and 14 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lakowicz et al., U.S. Patent No. 5,631,169.

The Office Action dated August 17, 2000 states that Lakowicz et al. discloses the use of polymeric supports for one reactant bound thereto and a second reactant supplied in solution or suspension. Further, the Office Action of August 17, 2000 states that samples are analyzed using first and second polypeptides, specifically antibodies, one of which is immobilized in the solid phase, and that each of the polypeptides is "labeled with different fluorescent labels that provide for assaying the modification of the polypeptides through the determination of the presence or absence of an antigen in the sample." Because energy transfer is used to monitor the interaction of antibody with antigen (the other antibody), the Office Action concludes that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

The Office Action dated April 19, 2001 states that "[t]he claim limitation 'covalent modification' is recited in the 'providing step', a step prior to the polypeptides being contacted with each other. No covalent interactions are required in claim 1. The covalent modification argued is not commensurate in scope with the now claimed invention that does not require that a covalent modification take place; the claim limitation defines a conditional relationship if a covalent modification is introduced to one of the two polypeptides." Applicants respectfully disagree.

As stated above in Applicant's response to the 35 U.S.C. § 102(b) rejection in view of the '797 patent, Applicants submit that claim 1, as amended, requires that at least one of the polypeptides of the polypeptide pair of claim 1 must be susceptible to covalent modification wherein the covalent modification modulates the association of the polypeptide with the other member of the polypeptide pair.

Lakowicz et al. do not teach a "polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**", as required by amended claim 1.

The Lakowicz reference teaches the interaction of two fluorescently labeled antibodies, one of which competes with an analyte for binding to the second antibody. There is no teaching of covalent modification of either antibody that modulates the interaction between the two antibodies.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. 102(b) rejection of claims 1-7 and 14 in view of Lakowicz et al.

Rejection of Claims 1-6, 10-12, 14 and 18 under 35 U.S.C. §102(e)

Claims 1-6, 10-12, 14 and 18 remain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Gallatin et al., (U.S. Patent No. 5,989,843 or 5,837,822).

Claims 1-6, 10-12, 14 and 18 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Gallatin et al., U.S. Patent No. 5,989,843 or 5,837,822. The Office Action dated August 17, 2000 states that Gallatin et al. discloses methods of analyzing samples utilizing a first polypeptide immobilized on a solid phase that interacts with a detectably labeled nonimmobilized binding partner, and that the presence or absence of bound label is correlated with the ability of a test agent to inhibit ICAM-R binding. Further, the Office Action of August 17, 2001 states that fluorescent polystyrene beads are disclosed for the immobilization of a first polypeptide, the second polypeptide is labeled with a radioactive label, and a scintillation proximity assay is used to identify modulators of the first polypeptide's association with the second polypeptide. The method is said to be useful for identifying modulators of ICAM-R binding, and it is concluded that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

The Office Action dated April 19, 2001 states that "[t]he claim limitation 'covalent modification' is recited in the 'providing step', a step prior to the polypeptides being contacted with each other. No covalent interactions are required in claim 1. The covalent modification argued is not commensurate in scope with the now claimed invention that does not require that a covalent modification take place. A component of the sample is not defined to function to covalently modify either one or both of the first or second polypeptides. The claim limitation defines a conditional relationship if a covalent modification is introduced to one of the two polypeptides." Applicants respectfully disagree.

Amended claim 1 claims "a method for **detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme** comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**; b) immobilizing the first polypeptide to a physical support; c) contacting the immobilized polypeptide with the second polypeptide; d) contacting said immobilized polypeptide and said binding partner polypeptide with said sample; and e) assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide.

Support for the inclusion of the phrase "analyzing a sample for the presence of a modifying enzyme" in amended claim 1, is provided in the specification at p. 3, lines 15-20, wherein it is stated that a "sample may contain one or more agents which are capable of modifying a polypeptide."

Support for the inclusion of the phrase "a method for detecting covalent modification of a polypeptide" is provided in Examples 1-12 of the specification, as each of these examples teaches such an assay.

Applicants submit that amended claim 1 requires the step of analyzing a sample for the presence of a modifying enzyme. Amended claim 1 also requires a polypeptide pair wherein covalent modification of at least one member of the polypeptide pair modulates the association of the polypeptides of the pair.

Applicants submit that Gallatin et al. does not teach either the polypeptide pair that is required by amended claim 1 or a "method for **detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme**", as recited in amended claim 1.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. 102(e) rejection of claims 1-6, 10-12, 14 and 18 in view of Gallatin et al. (U.S. 5,989,843 or 5,837,822).

Rejection of Claims 1 and 9 under 35 U.S.C. §102(b)

Claims 1 and 9 remain rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Sehr, U.S. Patent No. 5,341,215. The Office Action dated August 17, 2000 states that the reference discloses a method for analyzing a sample for the presence of biomolecules, the method comprising the use of a solid phase coated with capture molecules complementary to the biomolecules. The Office Action of August 17, 2000 further states that the biomolecules are antibody and antigen and are detected using surface plasmon resonance, concluding that the disclosure anticipates the presently claimed invention. Applicants respectfully disagree.

The Office Action dated April 19, 2001 states that "[t]he claim limitation 'covalent modification' is recited in the 'providing step', a step prior to the polypeptides being contacted with each other. No covalent interactions are required in claim 1. The covalent modification argued is not commensurate in scope with the now claimed invention that does not require that a covalent modification take place. A component of the sample is not defined to function to covalently modify either one or both of the first or second polypeptides. The claim limitation defines a conditional relationship if a covalent modification is introduced to one of the two polypeptides."

Amended claim 1 claims "a method for detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**; b) immobilizing the first polypeptide to a physical support; c) contacting the immobilized polypeptide with the second polypeptide; d) contacting said immobilized polypeptide and said binding partner polypeptide with said sample; and e) assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide.

Applicants submit that Sehr et al. does not teach "a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first**

polypeptide and said binding partner polypeptide," as required by claim 1 as amended. Specifically, similar to the previous references cited in the Office Action, the Sehr et al. reference does not teach covalent modification of at least one of the polypeptides, nor does it teach a covalent modification that "results in modulation of the association" and is "required for the association" of a first polypeptide and a binding partner polypeptide. Therefore, the reference does not teach all elements of amended claim 1. As such, Sehr et al. does not anticipate claim 1 as amended or claim 9 that depends from it.

In view of the above, Applicants respectfully request that the §102(b) rejection over Sehr et al. be withdrawn.

Rejection of Claim 17 under 35 U.S.C. §102(b)

Claim 17 remains rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,773,592 to Mills. The Office Action dated August 17, 2000 states that Mills discloses a polypeptide pair immobilized to a support, wherein the second polypeptide is bound to the first polypeptide, with the two polypeptides disclosed being "an enzyme immobilized (claim 24) covalently bound to either insulin (claim 25) or tissue plasminogen activator (claim 26)." According to the Office Action of August 17, 2000, the modulation of chemiluminescence "through energy transfer and photochromic excitation is in association with the first and second polypeptides," allegedly anticipating claim 17. Applicants respectfully disagree.

The Office Action of April 19, 2001 states that "[t]he two polypeptides of Mills function as a polypeptide pair that are bound to each other through a biocompatible polymer and are immobilized. Assaying of the polypeptide pair is detectable through the interactions of the polypeptides, and the luminide molecules. The modification of the glucose oxidase through binding of glucose, causes modulation of the binding of the insulin to the glucose oxidase through the release of the insulin from the polypeptide pair."

Amended claim 17 claims "a polypeptide pair comprising a first polypeptide immobilised to a support, and a second polypeptide bound to the first polypeptide, wherein, the binding of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the binding".

Mills teaches a polypeptide pair comprising insulin bound to glucose oxidase via a biocompatible polymer. The binding of glucose to glucose oxidase modulates the release of

insulin. Mills also teaches a polypeptide pair comprising tissue plasminogen activator bound to xanthine oxidase via a biocompatible polymer. The binding of xanthine to xanthine oxidase modulates the release of tissue plasminogen activator. Thus, Mills teaches modulation of the association of two polypeptides as a result of binding of a substrate to an enzyme. However, binding of a substrate to an enzyme (for example glucose to glucose oxidase or xanthine to xanthine oxidase) is not equivalent to a covalent modification of a protein since a substrate binds an enzyme via weak, non-covalent bonds.

Applicants submit that Mills does not teach "a polypeptide pair comprising a first polypeptide immobilised to a support, and a second polypeptide bound to the first polypeptide, wherein, the binding of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the binding", as claimed in amended claim 17 and cannot anticipate claim 17.

In view of the above, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claim 17 over Mills be withdrawn.

Rejection of Claims 1 and 20 under 35 U.S.C. §112, second paragraph

Claims 1 and 20 are rejected under 35 U.S.C. §112, second paragraph for alleged lack of clarity.

The Examiner states, that "the recitation of the word 'or' in section d) [of claim 1] does not distinctly claim Applicant's invention since "[i]t is not clear how the immobilized polypeptide **or** the binding partner polypeptide can be contacted with a sample when both polypeptides have already been contacted with each other". Applicants have amended claim 1 to replace "or" in step d) with "and".

The Examiner also states that "[c]laim 1 does not recite the covalent modification of the polypeptides, but defines a potential relationship between the polypeptides if one or both of them, at some future time, are covalently modified. Claim 1 has been amended to claim, "a method for **detecting covalent modification of a polypeptide** by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said**

association of said first polypeptide and said binding partner polypeptide". Applicants submit that amended claim 1 recites a positive covalent modification step.

The Examiner also states that it is unclear how claim 20 further limits the method of claim 1 since an enzymatic agent that would function to covalently modify any of the polypeptides of claim 1 has not been provided. The Examiner also states that "[i]f Applicant intends for a covalent modification to take place it should be recited in claim 1 through addition of method steps that positively recite covalent action by an agent.

Applicants submit that claim 1 has been amended to claim, "a method for **detecting covalent modification of a polypeptide** by analyzing a sample for the presence of a modifying enzyme comprising the steps of: a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide".** Thus, amended claim 1 provides a modifying enzyme in the sample to be analyzed. Amended claim 1 also recites a positive covalent modification step of at least one of the polypeptides of the polypeptide pair.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejection of claims 1 and 20.

Rejection of claims 1 and 20 under 35 U.S.C. §102(b)

Claims 1 and 20 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Avruch et al., U.S. Patent No. 5,582,995.

The Examiner states that "Avruch disclose a method of assaying a sample that utilizes the following components. The two polypeptides are a protein substrate containing a CAAX motif, (see claims 1, 7) and farnesyl-protein transferase. (see claim 1). The protein substrate is immobilized prior to contact with the sample (claim 19) and is susceptible to covalent modification (covalent farnesyl residue incorporation into the substrate polypeptide, see claims 7-9)."

Applicants submit that Avruch et al. teach a method of screening for compounds which inhibit the direct binding of Ras or Raf binding fragments of Ras, to Raf or Ras binding fragments of Raf.

Claim 1, as amended, claims "a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**".

Applicants submit that Avruch et al. do not teach a polypeptide pair wherein covalent modification of at least one of the polypeptides results in modulation of the association of the polypeptides of the pair, as required by claim 1. It is stated at column 6, line 50-column 7, line 6 of Avruch et al.,

> "Ras undergoes a series of sequential posttranslational modifications at its carboxyterminus, consisting of S-farnesylation at C_{186}, proteolytic cleavage after C_{186}, carboxymethylation of the C_{186} carboxyterminus, and palmitoylation at one or more cysteines upstream (Hancock, J. F. et al. Cell 57, 1167-1177 (1989)). When expressed in Spodoptera frugiperda (Sf9) cells, approximately 10% of the rasH polypeptide is associated with the membrane fractions, and a substantial portion of this has been shown to be palmitoylated, indicating that the Ras polypeptide has been fully processed. The cytoplasmic forms of baculoviral ras are not palmitoylated, although some molecules may be farnesylated (Page, M. J. et al. J. Biol. Chem. 264, 19147-19156 (1989)...At approximately equal concentrations, and under similar conditions, both the cytoplasmic and membrane-derived forms of Ras bound effectively to GST-Raf(1-257)...These data indicate that a fully processed Ras polypeptide is not essential for the binding of Ras to the Raf aminoterminal domain."

Thus, in view of the above, Avruch et al. do not teach all of the limitations of claim 1 and dependent claim 20, and do not anticipate these claims.

In view of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection of claims 1 and 20 in view of Avruch et al.

Rejection of Claims 1 and 20 Under 35 U.S.C. § 102(e)

Claims 1 and 20 are rejected under 35 U.S.C. § 102(e) for allegedly being anticipated by Josiah et al., U.S. 6,146,842.

The Examiner states, "Josiah disclose a method of assaying a sample that utilizes the following components. The two polypeptides are a protein substrate, (see claim 12) and farnesyl or geranylgeranyl transferase. (see claim 13) The protein substrate is immobilized prior to contact with the sample (claim 19) and is susceptible to covalent modification (see claim 14). The sample of Josiah is a test compound. (claim 12)."

Applicants submit that Josiah et al. teach an enzyme screen wherein a detectable moiety is attached to a substrate that comprises a chelating capturable moiety, which can be captured by an immobilized metal. According to the assay of Josiah et al., enzyme activity is detected by the presence of a detectable label on the reaction product immobilized on the solid phase.

Claim 1, as amended, claims "a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and **covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide**".

Applicants submit that Josiah et al. do not teach a polypeptide pair wherein covalent modification of at least one of the polypeptides results in modulation of the association of the polypeptides of the pair, as required by claim 1. The binding of the protein substrate to farnesyl or geranylgeranyl transferase results in covalent modification of the substrate. However, the covalent modification of the substrate does not modulate the binding of the substrate to the enzyme, as required by claim 1 and dependent claim 20.

Thus, in view of the above, Josiah et al. do not teach all of the limitations of claim 1 and dependent claim 20, and do not anticipate these claims.

In view of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) rejection of claims 1 and 20 in view of Josiah et al.

Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the outstanding Office Action have been addressed. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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Claims Marked to Show Changes:

1. (Twice Amended) A method for detecting covalent modification of a polypeptide by analyzing a sample for the presence of a modifying enzyme comprising the steps of:

a) providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association and is required for said association of said first polypeptide and said binding partner polypeptide;

b) immobilizing the first polypeptide to a physical support;

c) contacting the immobilized polypeptide with the second polypeptide;

d) contacting said immobilized polypeptide [or] and said binding partner polypeptide with said sample; and

e) assaying the modification of at least one of the polypeptides by measuring the association of the binding partner polypeptide to the first polypeptide.

8. (Twice Amended) The method of claim 1, wherein said association is measured by monitoring the molecular mass of the [species comprising the] binding partner polypeptide [associated] in association with the first polypeptide.

14. (Twice Amended) The method of claim 1, wherein the immobilised polypeptide is the polypeptide which is [susceptible to] covalently [modification] modified.

17. (Amended) A polypeptide pair comprising a first polypeptide immobilised to a support, and a second polypeptide bound to the first polypeptide, wherein,

the binding of the polypeptides is detectable, and

covalent modification of at least one of the polypeptides results in modulation of the binding and is required for said association of said first polypeptide and said binding partner polypeptide.